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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,144	08/04/2003	Jin Lee	TRA-006.01	5095

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FOLEY HOAG, LLP
PATENT GROUP, WORLD TRADE CENTER WEST
155 SEAPORT BLVD
BOSTON, MA 02110

EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
03/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/634,144	LEE ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 29-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,13-28 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-28-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 1-28-08 is acknowledged.

Claims included in the prosecution are 11, 13-28 and 32.

The examiner inadvertently indicated on PTOL-326 that claims 1-10 and 29-31 are allowed. They were withdrawn from consideration as drawn to non-elected invention.

In view of the amendments, the 102 rejection over Abra is withdrawn.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 12, 16, 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abra cited above, in view of Ye et al (5,997,899).

Abra discloses a method of preparation of liposomes containing cisplatin. The method involves dissolving cisplatin in sodium chloride solution and mixing the solution with a lipid mixture at 60-65 degrees. The liposomes were then extruded through filters and the temperature of the liposomes at this state is 20-30 degrees (Example 3).

What is lacking in Abra is the repetition of the heating and cooling. Abra does not teach the use of DPPC for the formation of liposomes

Ye et al while disclosing a method of preparation of liposomes teach that three

cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. One of the phospholipids taught is DPPC (Example 5).

To employ three cooling and heating cycles in the method of preparation of liposomes of Abra would have been obvious to one of ordinary skill in the art since Ye et al teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. The use of DPPC instead of HSPC taught by Abra would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since it is a commonly used phospholipid in the preparation of liposomes as shown by Ye et al.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Abra maintains the mixture at 60-65 degrees, followed by diafiltration and dialysis, then extrusion, but Abra does not cool the liposomes to room temperature until after the extrusion step. This argument is not persuasive. Instant claim 11 recites (a) combining an active platinum compound and a hydrophobic matrix carrying system; (b) establishing the mixture at a first temperature; and (c) thereafter establishing the mixture at a second temperature, which second temperature is cooler than the first temperature. As pointed out before, the method of Abra involves dissolving cisplatin in sodium chloride solution and mixing the solution with a lipid mixture at 60-65 degrees. The liposomes were then extruded through filters and the temperature of the liposomes at this state is 20-30 degrees (Example 3). Instant claims do not exclude the additional steps of Abra.

Applicant is incorrect in stating that the examiner has not provided some articulated reasoning with some rational underpinning for the skilled artisan to employ the temperature cycling of Ye, as required under KSR since according to Ye three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. This is clearly a rationale for one skilled in the art to employ three cycles. The motivation to combine need not be the same as applicants.

3. Claims 11-28 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamauchi (US2002/0182248) in combination with Abra and Ye et al both cited above.

Yamauchi teaches a method of encapsulating a drug in liposomes by mixing the lipids with an aqueous solution of a drug, heating it above the transition temperature of the membrane and then cooling it. The preparation is extruded through a membrane filter (0043, 0051 and 0057). What is lacking in Yamauchi is the use of cisplatin as the drug and also repeating the steps of changing the temperature in two or more cycles.

Abra as pointed out above, discloses a method of preparation of liposomes containing cisplatin. The method involves dissolving cisplatin in sodium chloride solution and mixing the solution with a lipid mixture at 60 to 65 degrees. The liposomes were then extruded through filters and the temperature of the liposomes at this state is 20-30 degrees (Example 3).

Ye et al as pointed out above, while disclosing a method of preparation of

liposomes teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. One of the phospholipids taught is DPPC (Example 5).

The use of a platinum drug such as cisplatin in the method of Yamauchi would have been obvious to one of ordinary skill in the art since Yamauchi teaches that any drug can be encapsulated and the reference of Abra shows the knowledge in the art of encapsulating cisplatin. To employ three cooling and heating cycles in the method of preparation of liposomes of Yamauchi would have been obvious to one of ordinary skill in the art since Ye et al teach that three cooling and heating cycles across the phase transition temperature facilitates drug equilibrium across the bilayer membranes. The use of DPPC would have been obvious to one of ordinary skill in the art with a reasonable expectation of success since it is a commonly used phospholipid in the preparation of liposomes as shown by Ye et al.

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues the following:

> "Yamauchi describes "liposomes and liposomal dispersions in which stability of drugs which have poor stability in the aqueous solution is improved." *Yamauchi* at ¶ 7. In particular, Yamauchi states that the stability of the aforementioned drugs becomes "markedly excellent when they are incorporated in liposomes prepared using a specified lipid," where the sphingolipid is "the main component of the liposomal membrane." *Id.* at ¶ 8-9. Example 1 of Ye discloses the preparation of sphingolipid liposomes by adding an aqueous solution of PGE 1 to evaporated sphingomyelin and heating to 60 °C. *Id.* at ¶ 57.

These arguments are not persuasive. Although Yamaguchi teaches PGE in the examples, his teachings pertain to any drug. With regard to the specific lipid, sphingolipid in Yamaguchi as argued by applicant, the examiner points out that claim 11 does not recite any specific phospholipid and thus, does not exclude sphingomyelin.

Furthermore, applicant has not provided any reasoning as to why liposome made with other phospholipids such as DPPC taught Yamaguchi would not behave the same way as the sphingomyelin containing liposomes. Applicant's arguments with regard to Abra are not persuasive since as pointed out above, instant claims do not exclude the liposomes comprising lipids specifically derivatized with hydrophilic polymer chains. Instant claim 11 does not recite any specific lipids. The examiner has already addressed applicant's arguments with regard to Ye.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is

(571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore, Ph.D/
Primary Examiner, Art Unit 1612

GSK